Hematologic Manifestations Of Tuberculosis

These discussions are selected from the weekly staff conferences in the Department of Medicine, University of California Medical Center, San Francisco. Taken from transcriptions, they are prepared by Drs. Martin J. Cline and Hibbard E. Williams, Assistant Professors of Medicine, under the direction of Dr. Lloyd H. Smith, Jr., Professor of Medicine and Chairman of the Department of Medicine.

DR. SMITH*: The Medical Grand Rounds this morning are, as you notice, in the general area of infectious disease. The first case, that of Mr. A, will be presented by Dr. Terry Andrew.

DR. ANDREW*[1]: The patient, Mr. A, is a 50-year-old white married building contractor who came to the University Medical Center for evaluation of a fever of about seven months' duration. He was in good health until November 1965, when he had the first of a series of episodes of severe pain in the left upper quadrant of the abdomen, and nausea. These symptoms were followed in a few days by fever and generalized malaise. The patient described the pattern of the fever as follows: The episodes would last for approximately one week, and recurred at approximately four-week intervals with temperatures in the range of 38.3° to 40.6°C (101° to 105°F). He went to a physician in January 1966 because of persistence of these symptoms. At that time axillary and inguinal adenopathy were noted. Laboratory data included hemoglobin of 12.2 gm per 100 ml, accelerated sedimentation rate, increased concentration of serum gamma globulin, a positive tuberculin and negative coccidioidin skin test. In March 1966 the patient was operated upon for an incarcerated incisional hernia, and an exploratory laparotomy was performed with observations described as "within normal limits."

Following operation the patient felt well until May 1966, when fever recurred and was associated with night sweats. In June he was admitted to a hospital in Stockton for further evaluation. It was found that he had lost approximately 13 pounds since the onset of symptoms. Body temperature at the time of admission was 38.3°C (101°F). On physical examination hepatomegaly and lymphadenopathy were noted and there was some question of a left retroperitoneal mass. Laboratory data at that time included hemoglobin of 9.3 gm per 100 ml of blood and leukocytes numbering 1,450 per cu mm with 30 per cent polymorphonuclear cells and 68 per cent lymphocytes. Examination of aspirated bone marrow showed myeloid hyperplasia and erythroid hypoplasia. No cause could be found for the fever and the patient was referred to the University of California Hospital, San Francisco. At that time no history could be obtained of cough, pleurisy, hemoptysis or production of sputum. The family history was negative. The patient said he smoked approximately one pack of cigarettes a day.

On physical examination the only abnormalities noted were slight adenopathy in the inguinal and axillary regions, hepatomegaly and questionable splenomegaly. Hemoglobin content was 8.7 gm per

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100 ml of blood, and leukocytes numbered 3,400 per cu mm—30 per cent polymorphonuclear cells, 65 per cent lymphocytes, 3 per cent monocytes and 2 per cent basophils. Platelet count was 301,000 per cu mm, with reticulocytes 2.1 per cent of the total. Results of urinalysis were within normal limits. Additional hematologic data included haptoglobin of 325 mg per 100 ml (normal), leukocyte alkaline phosphatase of 62 units (normal), prothrombin time of 40 per cent with a normal partial thromboplastin time, negative Sia water test and serum iron of 31 mcg per 100 ml, with a total iron-binding capacity of 230 mcg per 100 ml. The bone marrow at this time showed generalized hyperplasia, predominantly of the erythroid series.

Numerous bacteriologic cultures were taken of all available secretions and excretions from every orifice. These were all negative for acid-fast bacilli, fungi and ordinary pathogens. At the time of this admission, skin tests were positive with purified protein derivative, questionably positive for histoplasmosis, and negative for coccidiomycosis and blastomycosis. An x-ray film of the chest showed fibrocalcific densities. Additional x-ray studies showed degenerative disc disease in the cervical spine. An intravenous pyelogram, barium enema studies, an upper gastrointestinal tract series and small bowel follow through and abdominal lymphangiograms were all within normal limits.

Additional data obtained included a liver scan and liver biopsy, neither showing abnormality. A scalene lymph node biopsy showed multiple confluent and epithelioid caseous granulomas, whereupon administration of isoniazid and paraaminosalicylic acid was begun. The patient improved on this therapeutic regimen. Cultures of the scalene nerve specimen grew a few acid-fast organisms.

DR. SMITH: Dr. Youker will discuss the x-ray findings.

DR. YOUKER*[2]: We saw no active pulmonary disease but there was evidence of old granulomatous disease. There are granulomas in the right upper lung field and some scattered granulomas in the right mid-lung field (Figure 1). The lateral film of the chest also showed these same granulomas.

DR. SMITH: This patient was referred to the hospital by Dr. Robert Talley of Stockton. I do not believe that he was able to be here today. We would like to present a second case which illustrates other aspects of the hematologic manifestations of tuberculosis. The summation will be given by Dr. Stuart Aaronson.

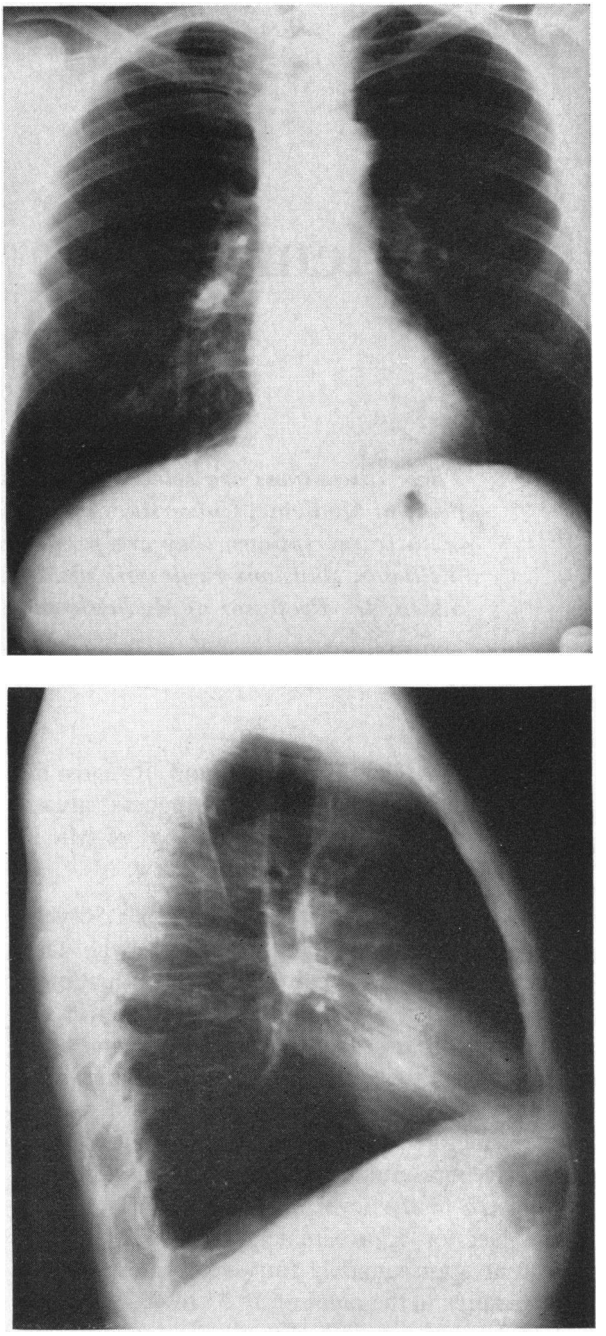

Figure 1.—*Upper*, x-ray film of lungs showing granulomas in upper right field and right mid-lung field. *Lower*, Lateral film of chest showing granulomas.

DR. AARONSON*[3]: The patient, Mr. B, is a 62-year-old painter with chief complaint of tenderness in the left upper quadrant of the abdomen, with

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weight loss and weakness of five months' duration. A mass in the left upper quadrant had been noted on routine physical examination in November 1965. In March 1966, the patient first noticed anorexia, weight loss and weakness. In June 1966, anemia was noted by a physician, and in August 1966 he was admitted to the University of California Medical Center. The patient is an employee of the Medical Center and for the past two years has had x-ray films of the chest taken every six months. These films have shown stable apical infiltrates. He was also known to have a positive purified protein derivative skin test. The patient has smoked about two and a half packages of cigarettes a day for the past 45 years; he has had a chronic non-productive cough, and in 1964 had an acute bleeding ulcer which responded to medical management.

On physical examination the patient was observed to be pale and cachectic. Body temperature was 38°C (100.4°F). Shotty lymphadenopathy was noted. The conjunctivae and mucous membranes were pale. Lung expansion was decreased bilaterally. The anteroposterior diameter of the chest was increased. There was dullness and increased fremitus on the right. Peristaltic movement was visible beneath a thin abdominal wall. The spleen, which was large and rock-hard, extended 8 cm below the costal margin, and there was a tender 2×3 cm nodule at the anterior margin. The liver edge was felt 4 cm below the right costal margin. It was nontender and firm. On examination of the extremities, early clubbing of the fingers and severe muscular wasting were noted.

Leukocytes numbered 16,000 per cu mm at the time of admission, with 60 per cent neutrophils and many immature cells, 10 per cent basophils and 10 per cent eosinophils. Packed cell volume was 19 per cent, the reticulocyte count 2.5 per cent of the total, and platelet count 80,000 per cu mm. Normoblasts were present in the peripheral blood.

X-ray examination revealed dense bones. Patchy apical infiltrates, which had increased since the previous examination, were noted on x-ray films of the chest. There was a large right pleural effusion. An intravenous pyelogram was within normal limits. A skin test with purified protein derivative was positive.

Thoracocentesis and pleural biopsy were performed. The latter revealed caseating granulomas. No intrabronchial lesions were seen at bronchoscopy. A bone biopsy was performed at the time of bronchoscopy when three previous marrow taps had been dry. The bone biopsy revealed sclerotic bone and myelofibrosis. Triple antituberculous therapy was begun and the patient was transferred to San Francisco County Hospital for continued treatment. Subsequently cultures for acid-fast bacilli of both sputum and pleural fluid were positive. The patient's condition has been stable at the county hospital.

DR. SMITH: Thank you very much, Dr. Aaronson. I have just been informed by the Radiology Department that with his transfer, the patient's films were also transferred, so we will not be seeing them this morning. With the two cases that have been summarized here as a starting point, there are many aspects of tuberculosis that could be presented. We have decided to concentrate on the hematological manifestations. I have asked Dr. Martin Cline to open the discussion.

DR. CLINE*[4]: Before embarking upon a general discussion of this subject, I would like to call attention to certain features of the clinical histories of these patients—in particular, the striking difference in the hematological manifestations. The first patient, A, had fever, anemia and severe leukopenia but with a relative and absolute increase in the lymphocyte count, when first observed. There were 60 to 70 per cent lymphocytes in the peripheral blood at a time when the number of leukocytes in the blood was in the range of 1,500 to 3,000 per cu mm. This observation is pertinent, in that Hodgkin's disease was considered in the differential diagnosis because it frequently produces adenopathy and a fever pattern of the type observed in this patient. A point against this diagnosis was the differential leukocyte count which would be extremely unusual in Hodgkin's disease where granulocytosis and lymphopenia are the rule. The clinical features in the second case were quite different, although this patient also had tuberculosis. He appeared to be a typical example of persons with myelofibrosis and myeloid metaplasia. He was cachectic, anemic, had a greatly enlarged liver and spleen and had dense bones. The initial radiologic reports suggested myelofibrosis. A peripheral blood smear (Figure 2) was characteristic of myeloid metaplasia, showing decided variation in the size and shape of the erythrocytes, the typical "tear drop" red cells and the

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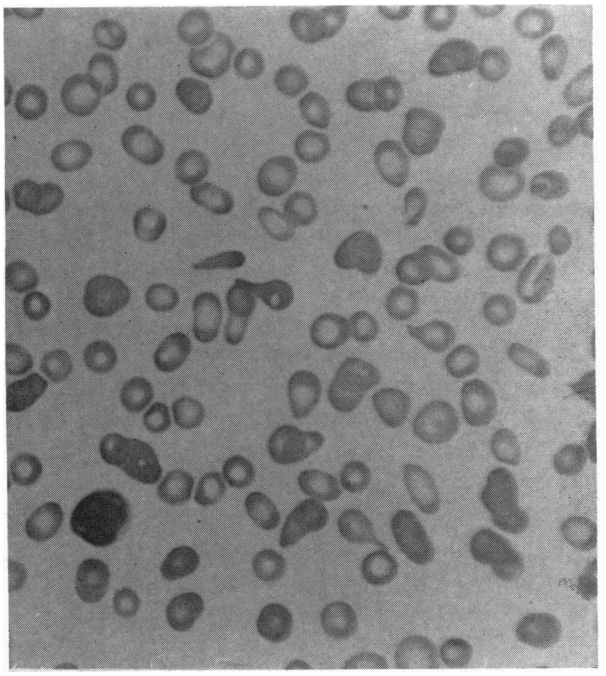

Figure 2.—Peripheral blood smear showing the teardrop forms and pronounced variation in size and shape of erythrocytes.

occasional fragmented or "helmet" cells also seen in this condition. Occasional giant platelets and nucleated red cells were also seen on the blood smear.

A pertinent feature of the history in this case is that two years before the patient was admitted to hospital he was seen by a reliable physician who did not observe either pallor or splenomegaly but seriously considered the diagnosis of active pulmonary tuberculosis. There is, then, indirect evidence that the tuberculous process preceded the hematologic manifestations in this patient.

Let us turn now to the hematologic manifestations of tuberculosis in those cases in which the hematologic changes are *not* the most prominent clinical feature (Table 1). I would like to extract two clinical pearls from that accumulation of statistics: (1) The incidence of various hematologic abnormalities is, with few exceptions, fairly low; (2) if the physician observes hemoglobin content of less than 10 gm per 100 ml of blood, he should look for extrapulmonary tuberculosis.

TABLE 1.—*Incidence of Various Hematologic Manifestations of Tuberculosis*

Abnormality	*Incidence (Per 100 Cases) in*	
	Pulmonary	*Miliary*
Anemia	17	60-80
Leukocytosis	10	.....
Leukopenia	10	.....
Monocytosis	35	.....
Lymphocytosis	4	.....
Eosinophilia	15	.....
Thrombocytopenia	rare	.....

And now, on to a consideration of each of the formed elements of the blood. Anemia, as I have observed, is quite rare in large series of cases of pulmonary tuberculosis, occurring in less than 20 per cent of patients with this disease. It is, however, quite common in disseminated and miliary tuberculosis, and occurs in between 60 and 80 per cent of cases. Leukocytosis and leukopenia are equally uncommon in tuberculosis and lymphocytosis is quite rare. Eosinophilia occurs in about 15 per cent of cases and is more common in pulmonary tuberculosis than in extra-pulmonary tuberculosis. The second patient presented this morning did have eosinophilia. Thrombocytopenia has been reported but its frequency is unknown. A very interesting observation is that monocytosis occurs not infrequently in tuberculosis. The older phthisiologists used the differential leukocyte count in predicting the clinical course of tuberculosis. They considered a rising lymphocyte count and a falling monocyte count to be a sign of poor prognosis, and a rising monocyte count a sign of good prognosis. While such observations have not stood the test of time, I was fortunate enough to come upon an interesting reference in the American Review of Tuberculosis of 1929 which reinforces my impression that the lung serves merely as a bellows to aerate the blood and that the hematology service should be expanded to encompass pulmonary diseases as well.

> In connection with the above studies we have formed the impression that an extension of the pathological process in a tuberculous lung usually manifests itself first in the blood picture, later by physical signs and x-ray, and often last of all by symptoms. (Flinn, J. W., and Finn, R. S., Ann Rev. Tuberc., 20:347, 1929.)

I would draw this quotation to the attention of Dr. Charles Carman and the members of the Pulmonary Disease Service.

If we consider situations in which the hematologic manifestations of tuberculosis dominate the clinical picture, the disease syndromes are three in number: (1) Leukemoid reactions, (2) myelofibrosis and myeloid metaplasia, and (3) pancytopenia which resembles that of aplastic anemia.

I would like to consider each of these. First, the leukemoid reactions. They are extremely rare, occurring in less than 3 per cent of cases of disseminated tuberculosis. The peripheral blood findings and the clinical features may be exactly the same as those of chronic myelocytic leukemia or, rarely, acute myeloblastic leukemia. Auer rods have been reported in some of these cases. Tuberculous leukemoid reactions and leukemia may be differentiated by a marrow chromosome preparation, which in the case of leukemia, will reveal an abnormal karyotype pattern. I would stress that in cases in which tuberculosis is associated with the hematologic picture of acute leukemia, it is likely that both diseases are present and that tuberculosis is complicating acute leukemia. The documented instances of tuberculosis producing the entire disease picture of acute leukemia are extremely rare.

Tuberculosis may be associated with pancytopenia and aplastic anemia. I have given the reference to an excellent article by Medd and Hayhoe.[1] They described a disease entity, tuberculous miliary necrosis with pancytopenia. In this disorder there are rather distinctive pathologic features with widespread miliary necrosis and very little tissue reaction. An outstanding clinical symptom is a high, spiking fever which the older phthisiologists called the "typhoidal variant" of tuberculosis. Leukopenia and splenomegaly are present. Tuberculous miliary necrosis with pancytopenia is a quite rare disease but it is important to be aware of its existence and to differentiate it from aplastic anemia of other causes. The clue to the diagnosis may be splenic enlargement, which is, of course, quite rare in typical aplastic anemia.

Tuberculosis may occur in all the myeloproliferative disorders. In the very first reported case of polycythemia vera, described in 1892 by Rendu and Widal, the patient had pulmonary tuberculosis, as did the patient in the second case reported some seven years later. In all, more than a hundred cases of pulmonary tuberculosis and polycythemia vera have been reported. The association was sufficiently frequent that older clinicians considered that the lipids of the tubercle bacilli might have erythropoietic activity. This, of course, is unlikely. Of all the myeloproliferative syndromes, it is myelofibrosis and myeloid metaplasia that has the most intriguing association with tuberculosis. There are a number of reasonably documented cases in which the myloid metaplasia followed the onset of tuberculosis as in the case of Mr. A, discussed today. The following is the "traditional" list of the causes of myelosclerosis and myeloid metaplasia found in most of the major textbooks of medicine and hematology:

MYELOSCLEROSIS AND MYELOID METAPLASIA

1. Agnogenic
2. Metastatic malignant disease
3. Chemical or radiation-induced injury
4. Marble bone disease
5. ? associated with tuberculosis

The majority of the cases are of unknown cause. There are a few due to marrow replacement by metastatic malignant lesions, a few from chemical or drug-induced marrow injury (for example, chloramphenicol and benzene) or radiation injury. A very few cases are due to a genetic abnormality in which the bones are dense—marble bone disease. In each of these lists of myelofibrosis the association with tuberculosis is questioned. I have listed a reference to the first description of myelofibrosis and myeloid metaplasia in the American literature.[2] The patient in the case described had tuberculosis of the mesenteric lymph nodes. It is quite interesting to read a description of this case, since it parallels closely Dr. Aaronson's description of the physical examination in the second case reported here today, that of Mr. B. In both cases the liver was extremely large and quite tender to palpation; and in both there were visible peristaltic waves in the left upper quadrant of the abdomen.

From my review I would make one point: In patients with associated myelofibrosis and tuberculosis, treatment of the acid-fast disease rarely restores the blood to normal. I think this is important in the prognosis of these diseases.

What are the possible causes of the association of tuberculosis and blood diseases. I think there are four possibilities. The first is that the association of a blood disorder and tuberculosis may be purely coincidental. The second is that the blood disorder favors the development of tuberculosis. There is little evidence to support such a thesis. In *untreated* hematologic diseases, infectious complications are usually caused by pyogenic organisms. The exception to this general rule is Hodgkin's disease. I think it was Ewing who said that "tuberculosis follows Hodgkin's disease like a shadow." The point I wish to stress, however, is that in the untreated patient with hematologic disease, tuberculosis is relatively rare.

A third possible explanation of the association of acid-fast organisms and blood disease is that treatment results in increased susceptibility to tuberculosis. This may be a real possibility. Patients are treated with corticosteroids and with alkylating agents which may suppress the normal immunologic responses and impair host resistance.

The fourth and last possibility is that tuberculosis causes the blood disease. If I may be permitted to speculate, I would say there are four possible ways in which tuberculosis could cause a reduction in circulating blood cells. First, as with any chronic infection, there may be suppression of erythropoiesis. Chronic infections produce "chronic simple anemias." These anemias are certainly chronic, but I do not think they are quite so simple. We do not understand their pathogenesis although we can document certain obvious abnormalities of erythropoiesis. In association with the anemia of chronic infection there is usually low serum iron and low iron-binding capacity. The plasma iron turnover rate is rapid but there is poor utilization of iron for erythropoiesis. Suppression of erythropoiesis by chronic infection would therefore be one type of blood disorder caused by acid-fast organisms. Tuberculosis can produce hypersplenism, and this might be a second cause of cytopenia. In essence, work hypertrophy of the spleen produces a large spleen which can sequester and destroy blood elements. A third possibility is that there is actual replacement of the marrow with tubercles and the associated fibrotic reaction. I think there is little evidence to support such an idea. The fourth possibility has to do with the fact that the drugs used in the treatment of tuberculosis may produce hematologic manifestations. Of this there is no doubt. The three major drugs used in the treatment of tuberculosis, isoniazid, para-aminosalicylic acid and streptomycin, may all individually or collectively produce pancytopenia or decreases of individual blood elements.

With this background we use the following guidelines in the approach to the association of tuberculosis and hematological disorders. First, that the possibility of tuberculosis exists in any case of myelofibrosis and myeloid metaplasia, aplastic anemia or atypical or poorly characterized blood disorder. In such a setting, one must make a painstaking search for acid-fast organisms by cultures of gastric aspirates, sputum, bone marrow and urine. In addition, the physician may be forced to consider biopsy of an enlarged lymph node, or, failing this, a "blind" biopsy of the scalenus anticus node. This last procedure was done successfully in the first case presented this morning.

I would like to turn from these clinical considerations for a moment to consider an equally important and perhaps more interesting aspect of the association between tuberculosis and anemia—the historical significance. This historical significance is based on the fact that it was the tuberculous rather thin, pale and languorous female who provided much of the visual imagery for the literature of the early and mid-19th century. I have already mentioned that significant anemia is uncommon in pulmonary tuberculosis and common in the extrapulmonary form of the disease.

Armed with this fact, I decided to do some research into the literature of musical opera and made, I think, some interesting observations. I was surprised to find that Mimi in *La Boheme* and Violetta in *La Traviata* are both described by the heroes as being "pale and wan." I would submit that this is *prima facie* evidence that these unconventional women had disseminated tuberculosis rather than pulmonary tuberculosis. Unfortunately the heroes of both these operas were rather frivolous characters and did not follow up this important observation.

To support my arguments for this historical significance of tuberculosis and anemia, I would like to read a few excerpts from a very interesting book by the brothers Dubos.[8] They are writing of a party in the home of Edgar Allen Poe in 1842, and in describing his wife they make use of a borrowed description and comment upon it:

" 'Dressed in white, delicately, morbidly angelic, Virginia was singing and playing the harp in the glow of the lamplight. Suddenly she stopped, clutched her throat, and a wave of crimson blood ran down her breast.' Although accidents such as this caused much anguish to Poe, he looked on his wife's illness as a source of a strange additional charm, which rendered more ethereal her chalky pallor and her haunted liquid eyes."

To William Cullen Bryant as to many others, the death of a beautiful girl was the most poetic of all themes, especially "if she died in the fall of the year of some obscure, slow and wasting malady." However, it was not alone the langourous female in the early Nineteenth Century who "profited" by the association of tuberculosis and anemia; some of the male artists and poets of that time also felt that it added to their glamour. In conclusion, one more excerpt from Dubos frères to support

this last argument: "Even the robust and sensuous Alexandre Dumas made occasional attempts to look frail and consumptive." [In 1823 and 1824] he writes in his memoirs, 'It was the fashion to suffer from the lungs. Everybody was consumptive, poets especially. It was good form to spit blood after each emotion, and to die before reaching the age of 30.' " Thank you.

DR. SMITH: Thank you Dr. Cline for spitting clinical pearls instead of blood before us this morning. We have time for some questions or comments. Dr. Carman, would you like equal time?

DR. CARMAN*[5]: Not now. Now that the incidence of the disease has fallen fairly sharply, I would emphasize the importance of recognizing the extrapulmonary manifestations of tuberculosis. This year we expect to have fewer than 300 new cases of tuberculosis found in San Francisco, a record low. Cases of the kind presented today are not an unusual occurrence in this hospital.

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Perhaps the most important point to be made about both extrapulmonary and pulmonary tuberculosis is the importance of chemoprophylaxis in the patients over 50 years of age who have had previously untreated active or inactive tuberculosis. This is the source or reservoir from which more than 60 per cent of cases of active tuberculosis derive. Shortly the Public Health Service will officially recommend that all such patients be given chemoprophylaxis with isoniazid for a minimum period of one year. In answer to Dr. Cline's comment about the importance of the blood as compared with the pulmonary system in this disease, I would persist in looking at the lungs as the window of the soul.

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